Single-center, open-label study with 14C-radiolabeled ACT-132577 to investigate the mass balance, pharmacokinetics, and metabolism following single oral administration to healthy male subjects.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Vascular hypertensive disorders
Study type	Interventional

Summary

ID

NL-OMON45381

Source
ToetsingOnline

Brief title
ACT-132577 Human ADME Study

Condition

- Vascular hypertensive disorders

Synonym
hypertension, PAH

Research involving
Human

Sponsors and support

Primary sponsor: Actelion Pharmaceuticals, Inc.
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: ACT-1352577, ADME

Outcome measures

Primary outcome

- Clinically relevant change from baseline to each time point of measurement in vital signs (supine blood pressure and pulse rate) after study treatment administration.

- Clinically relevant change from baseline to each time point of measurement in ECG variables: HR, and the intervals: PR, QRS, QT, RR, QTcB, and QTcF after study treatment administration.

- Clinically relevant change from baseline to EOS in clinical laboratory tests (clinical chemistry and hematology).

- Clinically relevant treatment-emergent ECG abnormalities from the study treatment administration up to EOS.

- Treatment-emergent AEs from the study treatment administration up to EOS.

- Treatment-emergent SAEs from the study treatment administration up to EOS.

- Mass balance (Cumulative excretion of radioactivity in urine and feces.)

- PK of 14C-radioactivity in whole blood and plasma

- PK of ACT-132577 and its metabolites in plasma

- Metabolic profiling (Profiles, identification, and quantification of metabolites in plasma, urine, and feces.)

Secondary outcome

Not applicable

Study description

Background summary

ACT-132577 is a new investigational compound that may eventually be used for the treatment of high blood pressure that is hard to treat (also called resistant hypertension). ACT-132577 is a metabolite of macitentan. Macitentan is registered under the tradename Opsumit® as a drug to treat pulmonary arterial hypertension (PAH) (high blood pressure in the arteries of the lungs). In the body, macitentan is metabolized (broken down) into ACT-132577. Macitentan and ACT-132577 are both active in the body. They act by binding to certain proteins on the cells that form the inside of blood vessels (the so-called endothelial cells).

ACT-132577 is in development and is not registered as a drug but has been given to humans before.

Study objective

The purpose of the study is to investigate how quickly and to what extent ACT-132577 is absorbed, distributed, metabolized (broken down) and eliminated from the body (this is called pharmacokinetics). ACT-132577 to be administered will be labeled with 14-Carbon (14C) and is thus radioactive (also called radiolabeled). In this way ACT-132577 can be traced in blood, urine and feces. It will also be investigated to what extent ACT-132577 is safe and tolerated.

Study design

The actual study will consist of 1 period during which you will stay in the clinical research center for 16 days (15 nights). You are expected at the clinical research center at 14:00 h in the afternoon prior to the day of administration of the study compound (Day -1; Day 1 is the day of administration of study compound). You will leave the clinical research center on Day 15.

You should take into account that it is possible that after your first 16-days stay in the clinical research center you may have to return for at most 2 additional stays of 24 hours each. In this study this is called the extended

observation period. Whether you have to participate in the extended observation period will depend on the amount of radioactivity that is still present in your urine and feces at the end of your stay in the clinical research center (Day 15). On Day 15 it is determined whether enough radioactivity has been recovered in urine and feces during the preceding 14 days. Also the amount of radioactivity excreted in urine and feces during the preceding 2 days (Day 13 and Day 14) is determined. If on Day 15 one of these results does not meet the predefined criteria, you will have to return on Day 18 (departure on Day 19) for a 24-hour stay. If on Day 18 the amount of radioactivity excreted still does not meet the predefined criteria, you will have to return again on Day 21 (departure on Day 22) for a 24-hour stay. You will be required not to have consumed any food or drinks (with the exception of water) during the 6 hours prior to arrival in the clinical research center on Day 18 and Day 21.

The post-study screening visit (the last time you will come to the clinical research center) will take place 1 to 2 days after your last stay in the clinical research center. You will be required not to have consumed any food or drinks (with the exception of water) during the 6 hours prior to arrival in the clinical research center. The appointment for the post-study screening visit will be made as soon as it is known when the study will end for you.

You will be contacted by telephone for a last safety follow-up call, 30 to 32 days after administration of the investigational compound. During this phone call you will be asked how you are feeling and if anything happened to you since the post-study screening visit.

Intervention

The volunteer will receive a single dose of 25 mg/3.7 MBq radiolabeled ACT-132577 as an oral capsule.

Study burden and risks

All drugs in development can potentially cause adverse effects; the extent to which this occurs differs. In medical practice, humans are being exposed to ACT-132577 as a metabolite of macitentan after administration of Opsumit®. Opsumit® is an approved drug at a dose level of 10 mg once daily.

ACT-132577 itself has been given to 56 healthy volunteers in a previous clinical study. In this study, ACT-132577 was given as single doses of 5, 25, 100, 300, and 600 mg and as multiple doses of 5, 25, and 100 mg once daily for 10 days. ACT-132577 was well tolerated in this study at all dose levels tested. The most frequently reported adverse effects following a single dose were headache, nausea, and a strong increase in heart rate upon standing up after sitting or lying down (orthostatic tachycardia). The most frequently reported adverse effect following multiple doses was headache. In addition, volunteers

that participated in the multiple dose part of the study reported sleepiness (somnolence), nasal congestion, nausea, upper respiratory tract infection, rash and a strong increase in heart rate upon standing up. All adverse effects were mild to moderate in intensity (this is the degree of discomfort caused by these adverse effects) and most had resolved by the end of the study visit.

In studies where rats and dogs were exposed to ACT-132577, the side effects included findings in the heart (only dogs), liver (rats and dogs), kidney (dogs only), nasal cavity (dogs only), and testes (rats and dogs). ACT-132577 belongs to a class of drugs that has been associated with decreases in blood laboratory parameters related to liver function and the amount of oxygen in the blood.

In this study radiolabeled ACT-132577 will be used. The amount of radioactivity in this dose will be approximately 3.7 MBq (MBq = megaBecquerel, this is a unit to express the amount of radioactivity in the study compound). The average environmental background radiation burden in The Netherlands is approximately 2 mSv per year (mSv = milliSievert, this unit indicates the burden on the human body; thus the effect on the human body of the amount of radioactivity administered). The additional radiation burden in this study due to the administration of approximately 3.7 MBq radiolabeled ACT-132577 is calculated to be 0.17 mSv. This is approximately 9% of the average annual radiation burden.

Contacts

Public
Actelion Pharmaceuticals, Inc.

Gewerbestrasse 16
Allschwil CH-4123
CH
Scientific
Actelion Pharmaceuticals, Inc.

Gewerbestrasse 16
Allschwil CH-4123
CH

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Healthy male volunteers
- 45-65 years, inclusive
- BMI: 18.0-28.0 kg / m2, inclusive
- SBP: 100-145 mmHg
- DBP: 50-90 mmHg
- HR: 45-90 bpm

Exclusion criteria

Suffering from hepatitis B, hepatitis C, cancer or HIV/AIDS. Treatment with another investigational drug within 3 months prior to screening or participation in more than 4 investigational drug studies within 1 year prior to screening. Loss of 250 mL or more of blood within 3 months prior to
screening. A radiation burden of > 0.1 milliSievert (mSv) and <= 1.0 mSv in the period of 1 year prior to screening; a radiation burden of >= 1.1 mSv and <= 2.0 mSv in the period of 2 years prior to screening, etc. (add 1 year per 1 mSv).

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	08-03-2017
Enrollment:	6
Type:	Actual

Ethics review

Approved WMO Date:	14-02-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-03-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2016-004175-44-NL
CCMO	NL60698.056.17